

## Acute and Chronic Effects of Amiodarone on Ventricular Refractoriness, Intraventricular Conduction and Ventricular Tachycardia Induction

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In eight patients, the right ventricular effective refractory period, rate-dependent changes in intraventricular conduction (as reflected by QRS duration during ventricular paced cycle lengths of 600 to 250 ms) and results of programmed ventricular stimulation were determined in the control state, 5 minutes after the intravenous infusion of 10 mg/kg body weight of amiodarone and after 2 months of treatment with oral amiodarone. The right ventricular effective refractory period was  $230 \pm 30$  ms (mean  $\pm$  SD) in the control study,  $248 \pm 27$  ms after intravenous amiodarone ( $p < 0.001$ ) and  $296 \pm 26$  ms after oral amiodarone ( $p < 0.001$ ). In the control state, QRS duration was constant at all paced cycle lengths. Intravenous amiodarone resulted in a rate-dependent prolongation of QRS duration. This rate-dependent prolongation was markedly accentuated by oral amiodarone in six patients who had an elevated serum level of reverse triiodothyronine ( $T_3$ ) after 2 months of oral treatment, but it was not more pronounced than the effects of intravenous amiodarone in two patients with a normal reverse  $T_3$  serum level after oral therapy. Both intra-

venous and oral amiodarone either suppressed or modified the induction of ventricular tachycardia by programmed stimulation in some patients, but in a discordant fashion. The relative effects of intravenous and oral amiodarone on ventricular refractoriness and conduction and on ventricular tachycardia induction did not correlate with serum amiodarone levels.

Chronic amiodarone therapy results in a marked prolongation in ventricular refractoriness compared with the relatively small but significant increase that occurs after intravenous amiodarone. Accentuation by oral amiodarone of the rate-dependent slowing of intraventricular conduction caused by intravenous amiodarone may be related to a direct electrophysiologic effect of amiodarone that is potentiated by an amiodarone-induced abnormality in thyroid hormone metabolism. The different effects of intravenous and oral amiodarone on ventricular tachycardia induction may be explained by different relative effects on refractoriness and conduction.

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The clinical response and results of programmed ventricular stimulation in patients with malignant ventricular arrhythmias treated chronically with oral amiodarone have been extensively studied (1-10). Much less information has been gathered on the acute effects of intravenous administration of amiodarone. Intravenous amiodarone was found to suppress ventricular arrhythmias in some studies (11-16), but not in others (17,18). It was reported not to prolong ventricular refractoriness significantly in studies (15,18,19) in which only a dose of 5 mg/kg body weight was used. One

prior study (18) compared, in the same patients, the acute and chronic effects of amiodarone on ventricular refractoriness and ventricular tachycardia induction, but the effects on tachycardia were evaluated in only three patients. Moreover, although the rate-dependent effects of amiodarone on intraventricular conduction have been studied in relation to acute intravenous administration (20), they have not been studied in relation to long-term oral administration.

Some investigators (21,22) have found that the therapeutic effects of amiodarone occur within a particular range of amiodarone serum levels, while others (23) have reported that an elevation in the serum level of reverse triiodothyronine ( $T_3$ ) correlates with amiodarone's therapeutic effect. The latter observation led to the suggestion that the effects of amiodarone may be at least in part related to the disturbance in thyroid hormone metabolism induced by amio-

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darone (24). However, no prior study has examined the relation between serum levels of reverse  $T_3$  and amiodarone's effects on ventricular refractoriness and conduction in humans.

The aim of the present study was to compare, in the same patients, the effects of high dose intravenous (10 mg/kg) and long-term oral amiodarone therapy on ventricular refractoriness, intraventricular conduction and ventricular tachycardia induction. In addition, the relation among the electrophysiologic effects and serum concentrations of amiodarone, its principal metabolite (desethylamiodarone) and reverse  $T_3$  were examined.

## Methods

**Patient characteristics.** The subjects of this study consisted of eight patients: five with recurrent, sustained ventricular tachycardia, two with out-of-hospital cardiac arrest and one with recurrent, nonsustained ventricular tachycardia. There were seven men and one woman, with a mean age of  $61 \pm 7$  years ( $\pm 1$  SD). All eight patients had coronary artery disease and a remote history of myocardial infarction. The mean left ventricular ejection fraction determined by contrast or radionuclide ventriculography was  $0.38 \pm 0.13\%$  (range 0.20 to 0.59). Before participation in this study, each patient underwent programmed ventricular stimulation and had inducible sustained ventricular tachycardia in the drug-free state. Before being treated with amiodarone, these patients underwent a mean of  $2.8 \pm 1$  drug trials that were ineffective in controlling ventricular tachycardia either clinically or during electropharmacologic testing.

**Electrophysiologic testing protocol.** After informed consent was obtained under a protocol approved by the Committee on Human Research at the University of Michigan, the patients were brought to the electrophysiology laboratory in the fasting, unsedated state after all antiarrhythmic drugs had been discontinued for at least four half-lives. Two quadripolar electrode catheters were inserted percutaneously into a femoral vein and positioned in the right ventricular apex and in the outflow tract or at the septum. Arterial blood pressure was monitored continuously with a 5F cannula inserted percutaneously into a femoral artery. Electrocardiographic leads  $V_1$ , I and III, the right ventricular electrograms and arterial blood pressure were displayed simultaneously on an oscilloscope and recorded at a paper speed of 25 to 150 mm/s with an Electronics for Medicine VR-16 recorder. Programmed ventricular stimulation was performed with a programmable stimulator (Bloom Associates, Ltd.) using stimuli with a current intensity of twice diastolic threshold and a duration of 2 ms. In every patient, the diastolic excitability threshold was 0.7 mA or less.

*Programmed ventricular stimulation* was performed initially at the right ventricular apex with single and double extrastimuli at two basic drive cycle lengths (usually 600 and 400 ms). If sustained ventricular tachycardia was not induced, stimulation was repeated at the right ventricular septum or outflow tract. This was followed by programmed ventricular stimulation with triple extrastimuli at the right ventricular apex and then at the second right ventricular site.

*Ventricular tachycardia* was defined as sustained if it had a duration of at least 30 seconds or required direct current countershock for termination. It was defined as nonsustained if it had a duration of six beats to 30 seconds. In each patient, sustained ventricular tachycardia was induced at least once in the control state. In five patients direct current countershock was needed to terminate the tachycardia and therefore this arrhythmia was induced only once before the administration of amiodarone. In three patients direct current countershock was not needed and ventricular tachycardia was induced at least twice in the baseline state.

*The duration of the QRS complex during ventricular pacing* was used as an index of intraventricular conduction. Incremental pacing was performed at the right ventricular apex at cycle lengths of 600, 500, 400, 350, 300, 275 and 250 ms for 15 to 20 complexes. The last several complexes of each pacing train were recorded at a paper speed of 150 mm/s. The effective refractory period at the right ventricular apex was then determined at a basic drive cycle length of 500 ms, immediately before the administration of amiodarone.

**Testing of intravenous amiodarone.** Amiodarone was administered intravenously in a dose of 10 mg/kg, at a rate of 50 mg/min. This resulted in a 10 to 20 mm Hg decrease in systolic blood pressure, but no patient developed symptomatic hypotension. The electrode catheter positioned at the right ventricular apex was not moved during the period of drug infusion. Five minutes after completion of the amiodarone infusion, determination of the effective refractory period at the right ventricular apex was repeated, followed by incremental ventricular pacing. The electrocardiographic standardization was the same as that used in the initial study. Programmed ventricular stimulation was then performed using a protocol identical to that used before drug administration. The end point of the stimulation protocol was the induction of sustained ventricular tachycardia. A blood sample for determination of the serum levels of amiodarone and desethylamiodarone was drawn when the stimulation protocol was completed (15 to 20 minutes after completion of the amiodarone infusion).

**Testing of oral amiodarone.** Oral amiodarone therapy was initiated at a dose of 1,200 mg/day for 5 days, followed by 800 mg/day for 1 month and then 600 mg/day for 1 month. No patient was treated with any other antiarrhythmic drug. After a mean of  $8.9 \pm 1$  weeks (range 8 to 10) of treatment with amiodarone (mean cumulative dose  $46.1 \pm 1.3$  g), an electrophysiologic study was repeated. An elec-

**Table 1.** Serum Levels of Amiodarone, Desethylamiodarone and Reverse T<sub>3</sub> After Intravenous and Oral Amiodarone Administration

| Case | Intravenous Amiodarone |                                 | Oral Amiodarone    |                            |                                 |
|------|------------------------|---------------------------------|--------------------|----------------------------|---------------------------------|
|      | Amiodarone (μg/ml)*    | Reverse T <sub>3</sub> (pg/ml)† | Amiodarone (μg/ml) | Desethylamiodarone (μg/ml) | Reverse T <sub>3</sub> (pg/ml)† |
| 1    | 3.9                    | 292                             | 1.5                | 1.2                        | 917                             |
| 2    | 4.2                    | 278                             | 0.9                | 0.5                        | 515                             |
| 3    | 4.8                    | 318                             | 1.9                | 1.2                        | 569                             |
| 4    | 2.7                    | 265                             | 3.2                | 2.6                        | 549                             |
| 5    | 4.1                    | 246                             | 1.9                | 1.1                        | 557                             |
| 6    | 2.9                    | 340                             | 2.2                | 1.4                        | 1,545                           |
| 7    | 4.5                    | 280                             | 2.6                | 2.8                        | 340                             |
| 8    | 3.5                    | 250                             | 1.7                | 1.2                        | 343                             |

\*Desethylamiodarone was not detected in any patient after intravenous amiodarone administration. †Normal range 80 to 350 pg/ml. T<sub>3</sub> = triiodothyronine.

trode catheter was positioned in the right ventricular apex such that the QRS complexes during ventricular pacing were similar in configuration to the paced QRS complexes in the baseline study. The right ventricular effective refractory period was determined at a basic drive cycle length of 500 ms and incremental right ventricular pacing was performed as in the baseline study to assess the rate-dependent effects of oral amiodarone on intraventricular conduction. Programmed ventricular stimulation was then performed using the same protocol as before. The end point of the stimulation protocol was one induction of ventricular tachycardia requiring direct current countershock or two or more inductions of sustained ventricular tachycardia that could be terminated by overdrive pacing. Programmed stimulation was performed at the same two right ventricular sites as in the baseline study. On completion of the electrophysiologic study, blood samples were drawn for determination of serum levels of amiodarone, desethylamiodarone and reverse T<sub>3</sub> (24 to 28 hours after the last oral dose of amiodarone).

**Data analysis.** The electrocardiographic lead with the most clearly defined onset and offset of the paced QRS complex was used to measure the QRS duration during

ventricular pacing. The same lead was used for all measurements in each patient. Patients in whom the onset or offset of the QRS complex was not well defined in any of the three monitored leads were not included in this study. The duration of the last QRS complex of each pacing train was measured independently in blinded fashion by two observers. Intra- and interobserver variability was less than 5%.

All statistical comparisons were performed with a paired *t* test. Values are expressed as mean  $\pm$  1 SD.

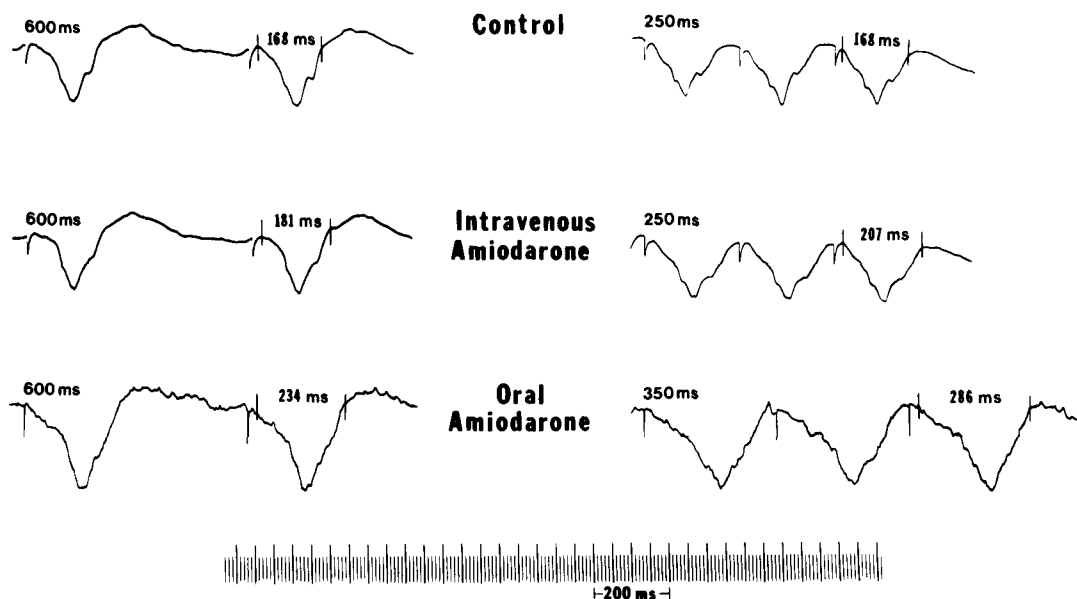
## Results

**Serum levels of amiodarone, desethylamiodarone and reverse T<sub>3</sub> (Table 1).** The mean serum level of amiodarone after intravenous amiodarone administration was  $3.8 \pm 0.7$  μg/ml; desethylamiodarone was not detected in any patient. After 2 months of treatment with oral amiodarone, the mean serum levels of amiodarone and desethylamiodarone were  $2.0 \pm 0.7$  and  $1.5 \pm 0.8$  μg/ml, respectively. The baseline mean reverse T<sub>3</sub> level was  $284 \pm 32$  pg/ml (normal range

**Table 2.** Effects of Intravenous and Oral Amiodarone Administration on Ventricular Refractoriness and Intraventricular Conduction

| Case | RVERP (ms) |     |      | QRS, PCL 600 ms (ms)* |     |      | QRS, Min PCL (ms)† |     |      | Min PCL (ms)‡ |     |      |
|------|------------|-----|------|-----------------------|-----|------|--------------------|-----|------|---------------|-----|------|
|      | C          | IV  | Oral | C                     | IV  | Oral | C                  | IV  | Oral | C             | IV  | Oral |
| 1    | 220        | 230 | 310  | 168                   | 181 | 234  | 168                | 207 | 286  | 250           | 250 | 350  |
| 2    | 210        | 240 | 270  | 160                   | 164 | 184  | 160                | 208 | 226  | 250           | 250 | 300  |
| 3    | 240        | 260 | 320  | 200                   | 227 | 260  | 260                | 255 | 294  | 275           | 275 | 350  |
| 4    | 200        | 210 | 270  | 127                   | 127 | 166  | 127                | 160 | 194  | 250           | 250 | 300  |
| 5    | 280        | 290 | 340  | 140                   | 147 | 174  | 140                | 160 | 194  | 300           | 350 | 400  |
| 6    | 260        | 270 | 300  | 114                   | 114 | 134  | 114                | 140 | 143  | 250           | 275 | 400  |
| 7    | 190        | 220 | 270  | 180                   | 183 | 186  | 180                | 220 | 214  | 250           | 250 | 275  |
| 8    | 240        | 260 | 290  | 173                   | 193 | 190  | 173                | 227 | 203  | 250           | 275 | 350  |

\*QRS duration at a ventricular paced cycle length (PCL) of 600 ms; †QRS duration at the minimal (Min) paced cycle length resulting in complete ventricular capture; ‡minimal paced cycle length resulting in complete ventricular capture. C = control; IV = intravenous; PCL = paced cycle length; RVERP = right ventricular effective refractory period.



**Figure 1.** Patient 1. The rate-dependent effects of intravenous and chronic oral amiodarone therapy on QRS duration. Shown are the last two to three QRS complexes of a train of 15 to 20 paced complexes. In the control state, the QRS duration was 168 ms at a paced cycle length of both 600 and 250 ms. After intravenous amiodarone, QRS duration increased by 8% to 181 ms at a paced cycle length of 600 ms and by 23% to 207 ms at a paced cycle length of 250 ms. The rate-dependent prolongation in QRS duration was markedly accentuated after 2 months of treatment with oral amiodarone. At a paced cycle length of 600 ms, QRS duration increased by 39% over control (to 234 ms) and increased by 70% to 286 ms at a paced cycle length of 350 ms. At paced cycle lengths shorter than 350 ms, there was 2:1 ventricular capture.

80 to 350). After 2 months of treatment with oral amiodarone, the mean reverse  $T_3$  level was  $667 \pm 397$  pg/ml.

**Effects on right ventricular effective refractory period (Table 2).** The baseline mean right ventricular effective refractory period was  $230 \pm 30$  ms. This value increased in each patient by 10 to 30 ms to a mean of  $248 \pm 27$  ms ( $p < 0.001$ ) after intravenous amiodarone therapy and increased by 40 to 90 ms over baseline to a mean of  $296 \pm 26$  ms ( $p < 0.001$ ) after chronic oral therapy. The mean ventricular effective refractory period after oral amiodarone was significantly greater than after intravenous amiodarone ( $p < 0.001$ ).

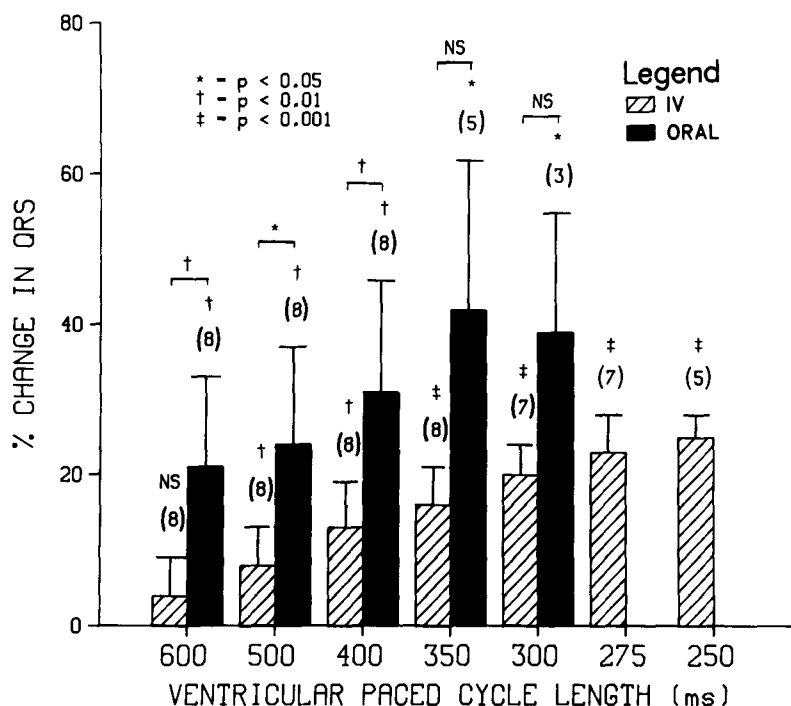
**Effects on intraventricular conduction (Table 2).** In the baseline state, QRS duration was the same at all ventricular paced cycle lengths, and the shortest paced cycle length associated with complete ventricular capture was  $260 \pm 19$  ms. After intravenous and oral amiodarone therapy, the shortest paced cycle length associated with complete ventricular capture was  $272 \pm 34$  ms ( $p > 0.05$  versus control) and  $341 \pm 46$  ms ( $p < 0.001$  versus control and intravenous amiodarone), respectively.

After intravenous amiodarone, there was a rate-dependent increase in QRS duration (Fig. 1). At a ventricular paced cycle length of 600 ms, QRS duration was unchanged compared with the control value ( $p > 0.05$ ), whereas at a paced cycle length of 250 ms, QRS duration increased by  $25 \pm 3\%$  ( $p < 0.001$ ) (Fig. 2).

After oral amiodarone therapy at a ventricular paced cycle length of 600 ms, there was also a rate-dependent increase in QRS duration (Fig. 1). The QRS duration increased by  $21 \pm 12\%$  over the control value ( $p < 0.01$ ) at a ventricular paced cycle length of 600 ms and increased by  $42 \pm 20\%$  ( $p < 0.05$ ) at a paced cycle of 350 ms (Fig. 2). At the shortest cycle length associated with complete ventricular capture, the QRS duration after oral amiodarone was increased by  $39 \pm 18\%$  over the pre-drug value ( $p < 0.01$ ). The increment over control in QRS duration at the shortest paced cycle length associated with complete ventricular capture was not significantly greater after oral amiodarone ( $39 \pm 18\%$ ) than after intravenous amiodarone ( $24 \pm 5\%$ ,  $p > 0.05$ ). At paced cycle lengths of 600, 500 and 400 ms, the magnitude of change in the QRS duration compared with control was greater after oral than after intravenous amiodarone ( $p < 0.05$ ) (Fig. 2). Examining the relative effects of intravenous and oral amiodarone on QRS duration, the effect of oral amiodarone was more pronounced in six patients (Cases 1 to 6) and not more pronounced in two patients (Cases 7 and 8, Fig. 3).

**Effects on ventricular tachycardia induction.** The configuration and cycle length of ventricular tachycardia induced in the control study are described in Table 3. After intravenous amiodarone, ventricular tachycardia became nonsustained in one patient and noninducible in two patients (Fig. 4). In these two patients (Cases 1 and 6), the coupling

**Figure 2.** The rate-dependent effects of intravenous and chronic oral amiodarone therapy on QRS duration. Shown is the percent change (compared with control) in the QRS duration at ventricular paced cycle lengths of 600 to 250 ms. Above each bar is shown 1 standard deviation. The numbers in parentheses refer to the number of patients who had complete ventricular capture at each paced cycle length. Values for oral amiodarone at cycle lengths of 275 and 250 ms are not shown because in only one patient was there complete ventricular capture at these cycle lengths. Statistical comparisons were performed with a paired *t* test. The percent changes in QRS duration after intravenous (IV) and oral amiodarone are compared with control and with each other. NS = not significant.



intervals that resulted in the induction of tachycardia in the control state no longer resulted in ventricular capture after intravenous amiodarone. Among the other five patients with inducible sustained ventricular tachycardia, the arrhythmia was of the same configuration as in the control study in three patients and of a different configuration in two. In the six patients who had inducible ventricular tachycardia after intravenous amiodarone, the ventricular tachycardia cycle length was unchanged in one, shortened in one and lengthened in four patients (Table 3).

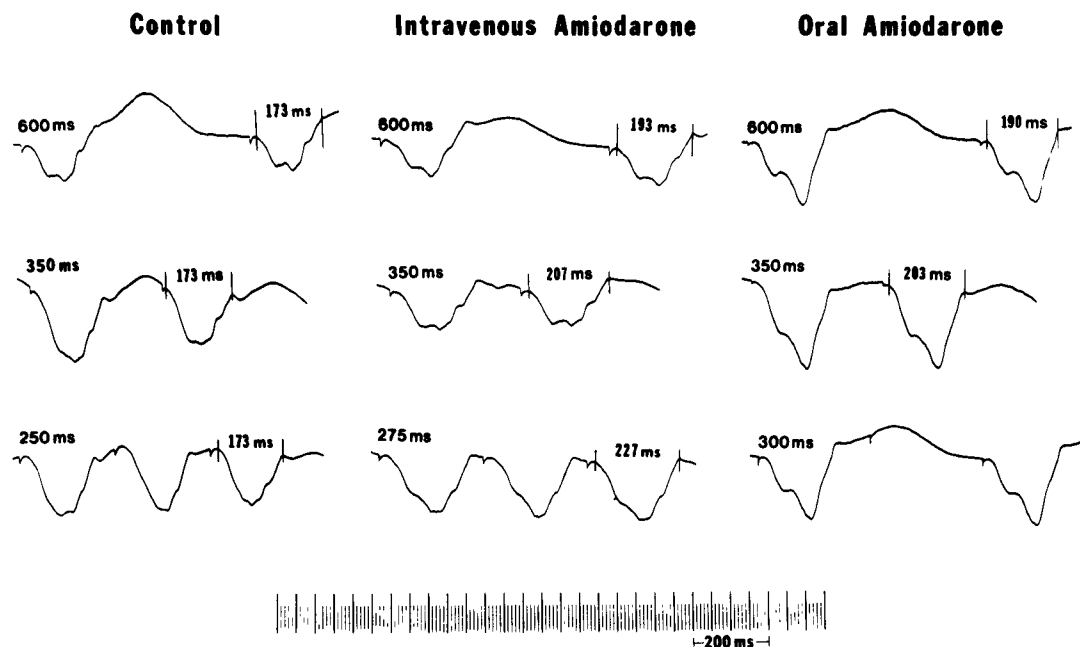
*The effects of oral amiodarone on ventricular tachycardia induction were different from the effects of intravenous amiodarone.* The three patients who had either noninducible or nonsustained ventricular tachycardia after intravenous amiodarone all had inducible sustained ventricular tachycardia after oral amiodarone, as did three others (Table 3). In Patients 1 and 6, coupling intervals that resulted in ventricular capture without ventricular tachycardia induction after intravenous amiodarone did result in tachycardia induction after oral amiodarone (Fig. 4). Two patients had inducible nonsustained ventricular tachycardia (Fig. 5). In only four patients was the configuration of the induced ventricular tachycardia after oral amiodarone the same as in the control study. In these patients, the coupling intervals of the extrastimuli that induced ventricular tachycardia were consistently 40 to 110 ms longer than the coupling intervals of the extrastimuli that induced tachycardia in the control state (Fig. 4). In every patient, the ventricular tachycardia cycle length was longer after oral amiodarone than in the control study (mean  $336 \pm 104$  versus  $240 \pm 90$  ms  $p <$

0.001). There was no discernible relation between the effects of intravenous or oral amiodarone on the right ventricular effective refractory period, intraventricular conduction and ventricular tachycardia induction.

**Relations among amiodarone, desethylamiodarone and reverse  $T_3$  serum levels and electrophysiologic effects.** In six patients (Cases 1 to 6), the QRS duration at comparable paced cycle lengths was greater after oral than after intravenous amiodarone. In each of these six patients, there was a large increase in the serum reverse  $T_3$  to levels of 515 to 1,545 pg/ml (Fig. 6). In contrast, in two patients (Cases 7 and 8) the QRS duration at comparable paced cycle lengths was not greater after oral than after intravenous amiodarone, and in both of these patients the serum reverse  $T_3$  level, although increased from baseline, was still within normal limits (Fig. 6). There were no other discernible relations among the serum levels of amiodarone, desethylamiodarone or reverse  $T_3$  and the electrophysiologic effects of intravenous or oral amiodarone.

## Discussion

**Relative effects of intravenous and oral amiodarone.** Our results demonstrate that both intravenous and oral amiodarone prolong the ventricular effective refractory period and slow intraventricular conduction in a rate-dependent fashion, but usually to different degrees. After 2 months of oral amiodarone therapy, the ventricular effective refractory period is consistently prolonged by 30 to 80 ms beyond the 10 to 30 ms increase that occurs acutely after



**Figure 3.** Patient 8. The rate-dependent response of QRS duration to intravenous and chronic oral amiodarone therapy. Shown are the last two to three QRS complexes of a train of 15 to 20 paced complexes. In the control state, QRS duration was not rate dependent; that is, QRS duration was 173 ms at paced cycle lengths of 600, 350 and 250 ms. After intravenous amiodarone, at a paced cycle length of 600 ms, there was a 12% increase in QRS duration to 193 ms. At paced cycle lengths of 350 and 275 ms, QRS duration increased by 20 (to 207 ms) and 31% (to 227 ms), respectively. There was 2:1 ventricular capture at a paced cycle length of 250 ms after intravenous amiodarone. After 2 months of oral amiodarone, there was 2:1 ventricular capture at paced cycle lengths of 300 ms and less. At paced cycle lengths of 600 and 350 ms, the QRS duration was similar to the values obtained after intravenous amiodarone. The serum level of reverse triiodothyronine ( $T_3$ ) was 250 pg/ml when intravenous amiodarone was tested and 343 pg/ml when oral amiodarone was tested (normal range 80 to 350 pg/ml).

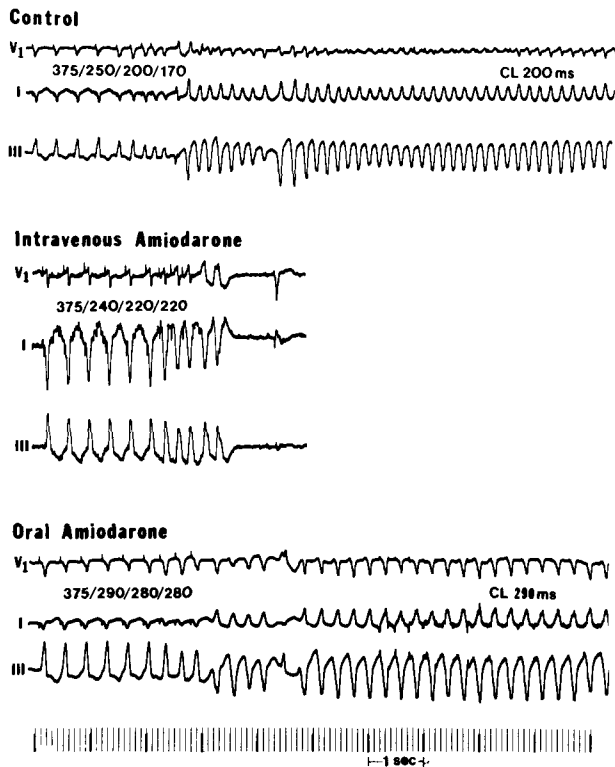
intravenous amiodarone. In contrast, the rate-dependent slowing of intraventricular conduction that occurs acutely after intravenous amiodarone is not consistently accentuated after oral amiodarone. The variable response of ventricular refractoriness and intraventricular conduction to intravenous and oral amiodarone suggests that different mechanisms may underlie the relative effects of intravenous and oral amiodarone on refractoriness and conduction.

**Effects on ventricular refractoriness.** A prior study (23) suggested that amiodarone's electrophysiologic effects on the myocardium may be mediated by a disturbance in thyroid hormone metabolism. Prolongation of the QT interval and suppression of ventricular premature depolarizations during treatment with oral amiodarone were found to correlate with elevation in the serum level of reverse  $T_3$ . An increase in the serum level of reverse  $T_3$  during therapy

**Table 3.** Effects of Intravenous and Oral Amiodarone Administration on the Induction of Ventricular Tachycardia

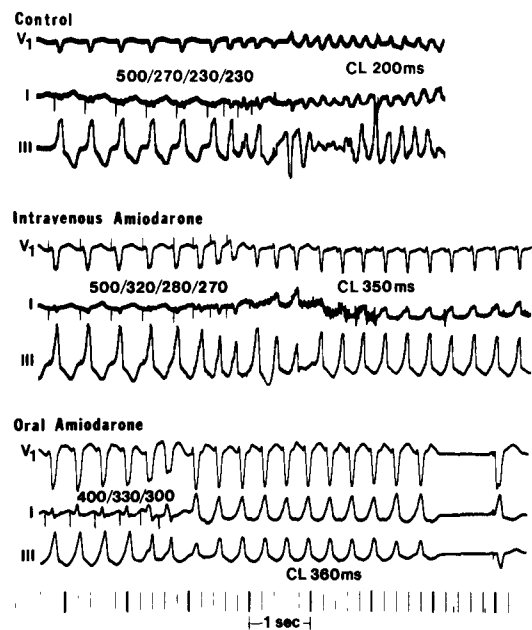
| Case | Induced Ventricular Tachycardia |         |           |                        |         |           |                 |         |           |
|------|---------------------------------|---------|-----------|------------------------|---------|-----------|-----------------|---------|-----------|
|      | Control Study                   |         |           | Intravenous Amiodarone |         |           | Oral Amiodarone |         |           |
|      | Form                            | CL (ms) | No. of ES | Form                   | CL (ms) | No. of ES | Form            | CL (ms) | No. of ES |
| 1    | RBBB                            | 200     | 3         | No VT                  | —       | —         | Poly            | 300     | 2         |
| 2    | RBBB                            | 190     | 3         | RBBB*                  | 230     | 2         | RBBB            | 250     | 3         |
| 3    | RBBB                            | 390     | 2         | LBBB                   | 360     | 2         | LBBB            | 480     | 2         |
| 4    | Poly                            | 150     | 2         | Poly                   | 180     | 2         | Poly*           | 210     | 3         |
| 5    | Poly                            | 200     | 3         | LBBB                   | 350     | 3         | LBBB*           | 360     | 2         |
| 6    | LBBB                            | 200     | 3         | No VT                  | —       | —         | LBBB            | 290     | 3         |
| 7    | RBBB                            | 375     | 2         | RBBB                   | 420     | 2         | RBBB            | 500     | 1         |
| 8    | RBBB                            | 220     | 3         | RBBB                   | 230     | 3         | LBBB            | 300     | 2         |

\*Only nonsustained ventricular tachycardia was inducible. CL = cycle length; ES = extrastimuli; LBBB = left bundle branch block configuration; Poly = polymorphic; RBBB = right bundle branch block configuration; VT = ventricular tachycardia.



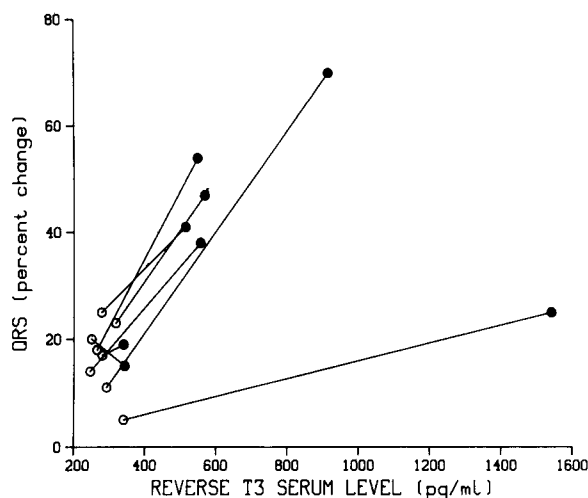
**Figure 4.** Patient 6. Results of programmed ventricular stimulation after intravenous and chronic oral amiodarone therapy. Three electrocardiographic leads (V<sub>1</sub>, I and III) are shown. In the control state, sustained ventricular tachycardia, cycle length (CL) 200 ms, which had a left bundle branch configuration and a superior axis, was induced by triple extrastimuli at the right ventricular outflow tract. Shown are the S<sub>1</sub>S<sub>1</sub>/S<sub>1</sub>S<sub>2</sub>/S<sub>2</sub>S<sub>3</sub>/S<sub>3</sub>S<sub>4</sub> coupling intervals that induced the ventricular tachycardia. After intravenous amiodarone there was not complete ventricular capture at the same coupling intervals that had induced ventricular tachycardia in the control study, and ventricular tachycardia was not inducible. Shown are the shortest S<sub>1</sub>S<sub>1</sub>/S<sub>1</sub>S<sub>2</sub>/S<sub>2</sub>S<sub>3</sub>/S<sub>3</sub>S<sub>4</sub> coupling intervals that resulted in complete ventricular capture at the right ventricular outflow tract. Two repetitive complexes were induced, but not ventricular tachycardia. After 2 months of treatment with oral amiodarone, sustained ventricular tachycardia, cycle length 290 ms, again with a left bundle branch configuration and a superior axis, was induced by triple extrastimuli at the right ventricular outflow tract. Note that the coupling intervals of the extrastimuli that induced ventricular tachycardia are considerably longer than in the control study.

with amiodarone reflects a block in the peripheral conversion of tetraiodothyronine (T<sub>4</sub>) to T<sub>3</sub>, and increased monodeiodination of T<sub>4</sub> to reverse T<sub>3</sub> (24). However, in our study, the serum level of reverse T<sub>3</sub> was not always elevated above the normal range after 2 months of treatment with oral amiodarone. Therefore, the larger increase in the ventricular effective refractory period that occurs after 2 months of oral treatment with amiodarone compared with that after intravenous treatment is unlikely to be attributable to a disturbance in thyroid hormone metabolism.



**Figure 5.** Patient 5. Results of programmed ventricular stimulation after intravenous and chronic oral amiodarone therapy. Shown are electrocardiographic leads V<sub>1</sub>, I and III. In the control state, sustained polymorphic ventricular tachycardia, cycle length (CL) 200 ms, was induced by triple extrastimuli at the right ventricular outflow tract. Shown are the S<sub>1</sub>S<sub>1</sub>/S<sub>1</sub>S<sub>2</sub>/S<sub>2</sub>S<sub>3</sub>/S<sub>3</sub>S<sub>4</sub> coupling intervals that induced the ventricular tachycardia. After intravenous amiodarone, sustained ventricular tachycardia was still inducible with triple extrastimuli but was modified to have a left bundle branch configuration, inferior axis and a cycle length of 350 ms. After 2 months of treatment with oral amiodarone, ventricular tachycardia was not inducible at a basic drive cycle length of 500 ms. However, with a basic drive cycle length of 400 ms and double extrastimuli at the right ventricular outflow tract, nonsustained ventricular tachycardia (cycle length 360 ms, left bundle branch configuration with an inferior axis) was reproducibly induced. Triple extrastimuli also resulted in nonsustained ventricular tachycardia.

Amiodarone has been demonstrated to acutely prolong action potential duration in a guinea pig papillary muscle preparation (25). The observation that intravenous amiodarone significantly prolongs ventricular refractoriness suggests that amiodarone also has a direct effect on action potential duration in ventricular myocardium in humans. Potentiation of this effect by oral amiodarone cannot be explained by differences in the serum level of amiodarone, because the amiodarone serum level was consistently higher during testing of intravenous amiodarone than during testing of oral amiodarone. Possible explanations for the greater increase in ventricular effective refractory period after oral compared with intravenous therapy include 1) a higher tissue level of amiodarone after long-term administration; 2) accumulation during chronic oral therapy of desethylamiodarone, which is not detectable acutely after administration of intravenous amiodarone and which may have a direct



**Figure 6.** Relation between QRS prolongation by intravenous and chronic oral amiodarone therapy and the reverse  $T_3$  serum level in eight patients. On the **ordinate** is the percent change (over control) in the QRS duration measured at the same ventricular paced cycle length for both intravenous and oral amiodarone. The ventricular paced cycle length used was the shortest one resulting in complete ventricular capture after treatment with oral amiodarone. Note that in two patients whose reverse  $T_3$  serum level was still within the normal range (80 to 350 pg/ml) after treatment with oral amiodarone there was no appreciable augmentation of QRS prolongation by oral compared with intravenous amiodarone. **Open circles** = intravenous amiodarone; **closed circles** = oral amiodarone.

electrophysiologic effect independent of amiodarone's effects; and 3) a time-dependent factor in amiodarone's membrane effects.

Whereas prior studies (18,19) have demonstrated that intravenous amiodarone acutely prolongs refractoriness in the atrioventricular node and in accessory atrioventricular connections, an acute effect on ventricular refractoriness has not been previously demonstrated (15,18,19). However, prior studies utilized a dose of intravenous amiodarone of 5 mg/kg, whereas a dose of 10 mg/kg was used in our study.

**Effects on intraventricular conduction.** In an isolated papillary muscle preparation, amiodarone was found (25) to block sodium channels in a rate-dependent fashion and to thereby decrease the maximal rate of rise of the action potential upstroke. Because intraventricular conduction depends predominantly on the fast sodium current, prolongation of intraventricular conduction would also be expected to occur in a rate-dependent fashion. A rate-dependent prolongation of intraventricular conduction, as reflected by changes in QRS duration during ventricular pacing, was demonstrated in response to intravenous amiodarone in a prior study (20) and confirmed in the present study. This rate-dependent slowing of intraventricular conduction was markedly accentuated after long-term treatment with oral amiodarone in some patients, but not in others. Augmen-

tation of the effects of amiodarone on intraventricular conduction after long-term therapy correlated not with the serum levels of amiodarone or desethylamiodarone, but with an elevation in the serum level of reverse  $T_3$ . In each patient whose reverse  $T_3$  serum level was elevated beyond the normal range after 2 months of treatment with amiodarone, slowing of intraventricular conduction was more pronounced by oral than by intravenous amiodarone. In contrast, in both patients who had a normal serum level of reverse  $T_3$  after 2 months of amiodarone therapy, the effects of oral amiodarone on intraventricular conduction were similar to the effects of intravenous amiodarone. This suggests that the direct effects of amiodarone on intraventricular conduction may be potentiated indirectly by its effects on thyroid hormone metabolism.

By blocking the peripheral conversion of  $T_4$  to  $T_3$ , or by competing with  $T_3$  binding to nuclear receptor sites, or both, amiodarone (or desethylamiodarone) may induce a state of hypothyroidism (24,26). The principal electrophysiologic effect of hypothyroidism on the action potential is to prolong its duration (24). Prolongation of the action potential duration (as might occur secondary to an amiodarone-induced disturbance in thyroid hormone metabolism) would be expected to prolong the period during which sodium channels are inactivated. Mason et al. (25) demonstrated that amiodarone blocks sodium channels that are in the inactivated state. To the extent that an increase in the serum level of reverse  $T_3$  reflects a state of hypothyroidism induced by amiodarone, our results are consistent with potentiation of amiodarone's blockade of sodium channels by a chronic increase in action potential duration. Alternatively, the apparent correlation between an elevated reverse  $T_3$  serum level and potentiation of an acute rate-dependent slowing of intraventricular conduction by oral amiodarone may simply reflect two independent end-organ effects that become more pronounced during long-term amiodarone therapy in some patients but not in others.

**Effects on ventricular tachycardia induction.** In the present study, intravenous amiodarone was found to be capable of either suppressing or modifying the induction of ventricular tachycardia by programmed stimulation. These results confirm the findings of Hariman et al. (15), who reported that intravenous amiodarone suppressed the induction of ventricular tachycardia in three of seven patients and converted sustained to nonsustained ventricular tachycardia in an additional two patients. The reason that amiodarone suppresses or modifies the induction of ventricular tachycardia in some patients but not in others is not clear; there was no discernible relation between the absolute or relative effects of amiodarone on the right ventricular effective refractory period or intraventricular conduction and its effects on the induction of ventricular tachycardia. However, any such conclusions are limited by the inability to determine amiodarone's effects on the actual substrate of the reentrant



circuit. Our present observations relate to refractoriness measured at the right ventricular apex and global intraventricular conduction. The effects of amiodarone on conduction and refractoriness within the reentrant circuit responsible for ventricular tachycardia could not be determined and may differ from its global effects.

The effects of oral amiodarone on the induction of ventricular tachycardia were discordant with the acute effects of intravenous amiodarone. In two patients in whom intravenous amiodarone completely suppressed the induction of ventricular tachycardia, sustained ventricular tachycardia was inducible after 2 months of oral treatment. Furthermore, in two patients who had inducible sustained ventricular tachycardia after intravenous amiodarone, only nonsustained ventricular tachycardia could be induced after oral treatment. These discordant responses to programmed stimulation are presumably due to a difference in the relative effects of intravenous and oral amiodarone on conduction and refractoriness within the reentrant circuit responsible for ventricular tachycardia. For example, induction of ventricular tachycardia after oral amiodarone by extrastimuli with coupling intervals that did not result in induction of ventricular tachycardia after intravenous amiodarone may be attributable to a greater degree of slowing of intraventricular conduction by oral amiodarone. Again, because the effects of amiodarone on the specific substrate for reentry were not determined, this explanation is speculative.

**Limitations.** 1) Although the duration of the QRS complex during ventricular pacing was used as an index of global intraventricular conduction, this is not a direct measure of intraventricular conduction. 2) The diluent in the intravenous form of amiodarone was Tween 80. The electrophysiologic effects of this diluent were not studied; therefore, its contribution to the changes observed after the administration of intravenous amiodarone is unknown.

**Conclusions.** The acute and chronic effects of amiodarone on ventricular refractoriness and conduction are different, perhaps because of a variable interplay between the direct and indirect effects of this agent on the myocardial action potential. Long-term amiodarone therapy results in a marked prolongation of ventricular refractoriness beyond the relatively small but significant increase that occurs acutely in response to intravenous amiodarone administration. This may reflect a direct effect of amiodarone that is accentuated by either higher tissue levels of amiodarone or accumulation of desethylamiodarone. Augmentation by oral amiodarone of the acute rate-dependent slowing of intraventricular conduction that occurs after intravenous administration appears to correlate with an increase in the serum level of reverse  $T_3$ , suggesting that effects on thyroid metabolism may potentiate sodium channel blockade by amiodarone. Both intravenous and chronic oral amiodarone can suppress or modify ventricular tachycardia induced by programmed stimulation, but in a discordant fashion, probably because

of different relative effects on conduction and refractoriness. Acute electropharmacologic testing with intravenous amiodarone therefore cannot be used to predict the response to programmed ventricular stimulation after long-term amiodarone therapy.

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